REMARKS

Applicants have carefully considered this Application in connection with the Examiner's Final Action, and respectfully request reconsideration of this Application in view of the above Amendment and the following remarks.

Applicants have cancelled Claims 4 and 79.

Applicants have amended Claims 1, 5, 8, 9, 10, 11, 76, 80, 83, 84, 85, and 86. Claims 1 and 76 have been amended to clarify that the vector, which is delivered into the muscle cells of a female mammal, is capable of expressing a growth hormone releasing hormone ("GHRH") or analog thereof. This amendment combines the limitations of canceled Claims 4 and 79 into the amended Claims 1 and 76, respectively. Claims 5 and 80 have been amended in order to maintain proper dependency from canceled Claims 4 and 79. Claims 8, 9, 10, 76, 83, 84, and 85 have been amended to either eliminate selected terms or to maintain proper antecedent basis of terms, as discussed in more detail below.

Claims 1, 5-13, 76, 80-88, 137 and 138 are pending.

1. **Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.**

Applicants wish to thank the Examiner for entering a compliant sequence into the record.

2. **Rejections Under 35 U.S.C. §112 second paragraph.**

Applicants wish to thank the Examiner for removing rejections based upon 35 U.S.C. §112 second paragraph.

3. **Rejections Under 35 U.S.C. §112 first paragraph.**

A. Enablement

Claims 1, 4-13 and 76, 79-88, 137, and 138 stand rejected under 35 U.S.C. §112, first paragraph, for being non-enabled. The Examiner asserts that the claimed invention encompasses *in utero* gene therapy, which is unpredictable, and that the specification does not provide sufficient guidance to enable any person skilled in the art to carry out the broadly claimed invention. However, the Examiner is of the opinion that a more limited claimed invention is enabled. For example, on Pages 2 and 3 of the current Office Action, the Examiner states:

"..because the specification, while being enabling for a method of improving or enhancing growth or rate of growth in an offspring of a pregnant non-human mammal female, comprising, introducing in the female sow intramuscularly during the third trimester of gestation of said offspring a vector comprising a muscle specific promoter operably linked to the nucleotide sequence disclosed in SEQID No.: 1 or SEQID No.: 8, wherein said nucleotide sequence is operably linked to a hGH3' untranslated region, wherein said nucleotide sequence is expressed in the female and wherein the expression of said nucleotide sequence results in improve or enhance growth or rate of growth of the offspring...."

In response, to the Examiner's assertion that the invention is overly broad, as to claim: *"...any nucleic acid linked to any promoter and any 3' UTR introduced at anytime into any animal..."* Applicants have amended the claims to read:

A method of improving or enhancing growth in an offspring from a female mammal comprising: introducing an effective amount of a vector into muscle cells of the female mammal prior to or during gestation of the offspring, wherein the vector is capable of expressing a growth hormone releasing hormone ("GHRH") or analog thereof in the female mammal during gestation; and wherein the vector comprises a promoter; a nucleotide sequence capable of expressing the GHRH or analog thereof; and a 3' untranslated region, under conditions that promote expression of the nucleotide sequence and wherein the introduction and expression of the nucleotide sequence results in improved or enhanced growth in the offspring and wherein the vector is not a viral vector.

Thus, the amended claims:

- do not claim any nucleic acid, but are limited to a nucleic acid encoding GHRH or analog thereof;
- do not claim any promoter, but are limited to a promoter that allows expression of the GHRH or analog thereof in muscle cells;
- do not claim any 3' UTR, but are limited to a 3' UTR that allows expression of the GHRH or analog thereof in muscle cells;
- do not claim any time of administration, but is limited to a period that is prior to or during gestation;
- do not claim any animal, but is limited to a female mammal.

B. In utero gene therapy

The Examiner is of the opinion that Applicants have provided arguments in the response to the previous Office Action, submitted on November 5, 2004, that supports the Examiner's position considering the unpredictability of "in utero gene therapy," for *"...any nucleic acid linked to any promoter and any 3' UTR introduced at anytime into any animal..."* (See Examiner's comments in the Office Action on Page 3, lines 7-19; Page 4, lines 1-22; Page 5, lines 1-22; and Page 7, lines 1-11).

Applicants submit that neither the original claims, nor the current claims, as amended, encompass "*in utero* gene therapy." Prior arguments presented were to clarify this point. Applicants submit that the method claimed DOES NOT introduce genetic material (nucleic acids) to the fetus directly or indirectly. As indicated previously, the genetic material delivered to the female mammal does not even appear to migrate away from the injection site, and therefore should not find its way into the fetus. Rather, genetic material is delivered to the diploid or muscles of a female mammal, which results in the subsequent expression of an encoded GHRH protein. Such expression apparently makes the female mammal a better incubating vessel for the fetus, which improves the growth and health of the offspring during gestation and after birth.

Thus, because Applicants' invention is not related to "in utero gene therapy," any rejections by the Examiner based on the evidence that "in utero gene therapy" as being not enabled are not relevant and should be withdrawn.

C. Gene Therapy (Zanjani and Anderson)

The Examiner is of the opinion that E. D. Zanjani and W. French Anderson described "*in utero* gene therapy ("IUGT")" as "**gene transfer in the fetus . . . .**" *See* "Prospects for In Utero Human Gene Therapy," *Science*, Vol. 285, page 2084, first column, 24 September 1999, which effectively demonstrates that there are several elements of gene therapy in which a skilled artesian has no control. The Examiner is further of the opinion that the Applicants' arguments or specification do not provide any specific guidance to address the issues of gene therapy at the time of filing the invention.

Applicants respectfully disagree. Applicants have provided specific examples having reproducible data in the specification (e.g. Example 14 in specification, page 42, paragraph [0146-0147]), which should supersede the previous failed attempts of the prior art at the time of the invention. Applicants have indicated in the amended claims that expression of a GHRH gene or analog thereof in muscle cells of a female mammal overcomes several common problems of expression that were specifically addressed in Zanjani and Anderson. In addition, the selection of genes in this application are related to the GHRH axis, which has a naturally regulated by feed-back mechanisms at multiple levels, which addresses the issue of gene regulation. The examples in the application show there were no adverse effects on the treated animals and their offspring (e.g page 50, paragraph [0159], page 57 , paragraph [0184]). However, in all treated animals in the studies described in the specification, published studies, and hundreds of other animals enrolled in different studies, no adverse effects linked to the plasmid were observed, as described. Furthermore, the results with this therapy are better than conventional therapies. The offspring from treated animals are slightly bigger at birth, thus more resistant to disease or other challenges. GHRH positively impacts the offspring immune function, and thus these animals are healthier. No antibiotic treatments or growth promotants are necessary. Lastly, feed efficiency is improved, so these

mammals are generating less manure, with positive impact on the environment. Applicants have limited the general term "animal" in the claims to a more specific term "mammals." Additionally, any non-mammalian specific species has been removed from dependant claims.

D. Gene Therapy (Khan)

The Examiner has indicated that Khan et al. (2002, Endrocrinology) and Khan et al., (2003, Amer. J. Physiol.) are references selected to illustrate that even "post-filing" studies have demonstrated examples that gene therapy, a general method, is unpredictable (Page 5, lines 3-12). The Examiner is of the opinion that a skilled artesian is NOT enabled for utilizing "any nucleic acid linked to any promoter and any 3'UTR introduced into any animal at any time by any method/route so as to increase growth of the offspring."

In response, Applicants have amended claims to address the issue of "any nucleic acid linked to any promoter and any 3'UTR introduced into any animal at any time...," as discussed in section A above.

E. Delivery Vectors (Stribley) et al. (2002, Fertility and Sterility)

The Examiner is of the opinion that Stribley et al., (2002, Fertility and Sterility) does not teach how the use of viral vectors function in a predictable manner. As such, Applicants also do not show how the claimed invention will function in a predictable manner if viral vectors are used.

Applicants have amended claims to remove viral delivery vectors.

F. Delivery Vectors (Romano) et al. (2000, Stem Cells).

The Examiner is of the opinion that Applicants' claims encompass Romano's "in utero gene therapy." Additionally, the Examiner has maintained his rejection in reference to the Romano reference because diploid cells include brain and skin cells and Applicants' specification does not teach that injection into diploid cells such as skin cells and brain cells would be successful vehicles for producing GHRH protein.

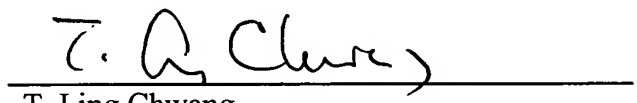
Applicants have amended claims to remove the mention of diploid cells.

4. Conclusion

Applicants respectfully submit that, in light of the foregoing Amendment and remarks, the amended claims are in condition for allowance. A Notice of Allowance is therefore respectfully requested.

If the Examiner has any other matters which pertain to this Application, the Examiner is encouraged to contact the undersigned to resolve these matters by Examiner's Amendment where possible.

Respectfully submitted,



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